fragmenting said ionized complex; and

determining whether highly ranked member or members binds to said molecular interaction site of said RNA.

REMARKS

Claims 19-23 and 26-35 are pending in the present application. Claims 19, 21, 26, 31, 32, and 34 have been amended. No new matter has been added. Upon entry of the present amendment, claims 19-23 and 26-35 will remain pending.

As a preliminary matter, Applicants acknowledge receipt of the "Attachment for PTO-948" outlining changes for prosecution of applications requiring drawing changes. The Examiner states that formal drawings are required in response to the Office Action. Applicants, however, have not filed formal drawings nor have they received a Notice of Patent Draftpersons's Patent Drawing Review (PTO-948) indicating that the submitted drawings need changes. Nonetheless, in an effort to expedite the application, formal drawings have been filed on date even herewith under separate cover to the Draftsperson. Originally filed drawing Figures 41 and 42 have each been divided into two figures and renumbered as Figures 41a, 41b, 42a, and 42b, respectively. The separation was necessary to allow enlargement of the mass spectrums for enhanced clarity. No new matter has been added to the drawings.

I. The Claimed Invention Is Novel

Claims 21-23, 26-28, and 31 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by the abstract of Romby *et al.*, *J. Biomol. Struct. & Dyn.*, **1987** *5(3)* 669-687 (hereinafter, the "Romby reference"). Applicants traverse the rejection and respectfully request reconsideration thereof since the Romby reference fails to teach each and every element recited in the rejected claims.

The Romby reference reports experimental and modeling based discovery concerning the T-loop of yeast $tRNA^{Asp}$. In particular, the Romby reference reports that the T-loop in tRNA possesses an intrinsic conformation that is governed by constant residues. The Romby reference reports that

the intrinsic conformation exists "primarily without the structural context of the entire tRNA molecule." In reaching this conclusion, the Romby reference reports that the constant length of the T-loop and the presence of ψ55 are "crucial for the correct interaction between the T- and D-loops" of tRNA.

A prior art reference anticipates a claim if each and every element of the claim appears in the prior art reference. *Glaxo Inc. v. Novopharm, Ltd.*, 52 F.3d 1043, 1047, 34 U.S.P.Q.2d 1565, 1567 (Fed. Cir. 1995). Applicants respectfully submit that the Romby reference does not disclose every element of the rejected claims.

Claims 21-23, 26-28, and 31 of the invention recite, *inter alia*, that a virtual library of compounds predicted or calculated to interact with the molecular interaction site is generated *in silico*. The Romby reference, however, does not teach the generation of a library of compounds to interact with a molecular interaction site. The Romby reference is concerned with the structure of the T-loop of tRNA and does not evaluate the ability of compounds to bind to the T-loop. The Romby reference's only mention of interactions with the T-loop being studied, as quoted by the Examiner, is the "interaction between the T- and D-loops." Studying the tertiary base pairing interactions between the T-loop and D-loop within tRNA is different from studying the interaction between a molecular interaction site of tRNA and a library of compounds. Therefore, the Romby reference does not teach the generation of a library of compounds to interact with a molecular interaction site.

Furthermore, claims 21-23, 26-28, and 31 of the invention recite that a molecular interaction site on the RNA is identified and a three-dimension representation of the site is compared to a virtual library of compounds. Claims 21-23, 26-28, and 31 recite, *inter alia*, the comparison is used to "generate a hierarchy of said compounds ranked in accordance with their respective ability to form physical interactions with said molecular interaction site." The Examiner states that the Romby reference's "analysis of variants resulted in defining the hierarchy of which ones contained residues 'crucial for the correct interactions between the T- and D-loops.'" However, the "variants" that the Examiner refers to in the Romby reference were not a variety of compounds that "interact with a molecular interaction site" within RNA as recited in the claims. Rather, the term "variants" in the

Romby reference pertains to a variety of tRNA that vary in sequence or length of the nucleotides within the T-loop. Therefore, the Romby reference does not teach the generation of a hierarchy of compounds ranked in accordance with their respective ability to bind with the molecular interaction site within tRNA.

Accordingly, Applicants respectfully request that the rejection of claims 21-23, 26-28, and 31 under 35 U.S.C. § 102(b) be withdrawn.

II. The Claims Are Clear And Definite

Claims 19-23 and 26-35 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as their invention. The Office Action asserts that the claim preamble indicates a method of "identifying a compound which modulates activity of a target RNA," but that the claims do not reveal such a compound, *per se*. Applicant has amended the claim language to clarify that the claim steps identify a compound that binds with the target RNA. The claims, however, are not limited to finding a single compound. Rather, the claim steps may identify a single compound that interacts with a molecular interaction site or a plurality of compounds.

In view of the amendment to the claims, Applicants respectfully request that the rejection under 35 U.S.C. § 112, second paragraph be withdrawn.

III. Conclusion

In view of the foregoing, Applicants respectfully submit that the claims are in condition for allowance. An early notice of the same is earnestly solicited. The Examiner is invited to contact Applicants' undersigned representative at (215) 564-8906 if there are any questions regarding Applicants' claimed invention. Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made**."

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Paragraph beginning at page 25, line 16 of the specification has been amended as follows:

[Figure 41 shows] Figures 41a and 41b show the ESI-CID-MS of a 27-mer RNA/DNA hybrid in the presence and absence of paromomycin.

Paragraph beginning at page 25, line 18 of the specification has been amended as follows:

[Figure 42 shows] Figures 42a and 42b show the ESI-MS of a 27-mer RNA/DNA hybrid target in the presence of paromomycin alone (panel a), and in the presence of both paromomycin and a combinatorial library (panel b).

Paragraph beginning at page 154, line 15 of the specification has been amended as follows:

Cleavage and fragmentation of the complex by CID afforded information regarding the location of binding of the paromomycin to the chimeric nucleic acid. CID was found to produce no fragmentation at the dA sites in the nucleic acid. Thus paromomycin must bind at or near all three dA residues. Paromomycin therefore is believed to bind to the dA bulge in this RNA/DNA chimeric target, and induces a conformational change that protects all three dA residues from being cleaved during mass spectrometry. See [Figure 41] Figures 41a and 41b.

Paragraph beginning at page 15, line 18 of the specification has been amended as follows:

The ESI mass spectrum so obtained, shown in [Figure 42] Figures 42a and 42b, demonstrated the presence of new signals for the (M-5H)5- ions at m/z values of 1897.8, 1891.3 and 1884.4. Comparing these new signals to the ion peak for the 27-mer alone the observed values of m/z of those members of the combinatorial library that are binding to the target can be calculated. The masses of the binding members of the library were determined to be 566.5, 534.5 and 482.5, respectively. Knowing the structure of the scaffold, and substituents used in the generation of this library, it was possible to determine what substitution pattern (combination of

substituents) was present in the binding molecules.

In the Claims:

Claims 19, 21, 26, 31, 32 and 34 have been amended as follows.

19. (Twice Amended) A method of identifying a compound [which modulates activity of] that binds to a target RNA comprising:

generating *in silico* a virtual library of compounds predicted or calculated to interact with a molecular interaction site within said RNA;

comparing three dimensional representations of said molecular interaction site with members of the virtual library of compounds to generate a hierarchy of said compounds ranked in accordance with their respective ability to form physical interactions with said molecular interaction site;

synthesizing the highly ranked members of said hierarchy of compounds; and

testing said highly ranked members to determine their ability to interact with said molecular interaction site by:

contacting the target RNA with at least one of said highly ranked members to provide a complex between the RNA and the member or members;

ionizing said complex;

fragmenting the ionized complex; and

determining whether highly ranked members bind to the molecular interaction site of said RNA.

21. (Twice Amended) A method of identifying a compound [which modulates activity of] that binds to a target RNA comprising:

identifying at least one molecular interaction site on said target RNA, wherein said target RNA comprises single-stranded RNA and is mRNA, pre-mRNA, tRNA, rRNA, or snRNA;

generating *in silico* a virtual library of compounds predicted or calculated to interact

with said molecular interaction site; and

comparing three dimensional representation of said molecular interaction site with members of the virtual library of compounds to generate a hierarchy of said compounds ranked in accordance with their respective ability to form physical interactions with said molecular interaction site.

26. (Amended) A method of identifying a compound [which modulates activity of] that binds to a target RNA comprising:

identifying at least one molecular interaction site on said target RNA by comparing the nucleotide sequence of said target RNA with the nucleotide sequence of a RNA from a different taxonomic species, identifying at least one conserved region, determining the secondary structure of said conserved region;

generating *in silico* a virtual library of compounds predicted or calculated to interact with said molecular interaction site; and

comparing three dimensional representation of said molecular interaction site with members of the virtual library of compounds to generate a hierarchy of said compounds ranked in accordance with their respective ability to form physical interactions with said molecular interaction site.

31. (Amended) A method of identifying a compound [which modulates activity of] that binds to a target RNA comprising:

identifying at least one molecular interaction site on said target RNA by comparing the nucleotide sequence of said target RNA with the nucleotide sequence of RNA from a different taxonomic species, identifying at least one conserved region, and determining the secondary structure of said conserved region, wherein said target RNA comprises single-stranded RNA and is mRNA, pre-mRNA, tRNA, rRNA, or snRNA;

generating *in silico* a virtual library of compounds predicted or calculated to interact with said molecular interaction site; and

comparing three dimensional representation of said molecular interaction site with members of the virtual library of compounds to generate a hierarchy of said compounds ranked in accordance with their respective ability to form physical interactions with said molecular interaction site.

32. (Amended) A method of identifying a compound that [modulates activity of] binds to a target RNA comprising:

identifying at least one molecular interaction site on said target RNA

generating *in silico* a virtual library of compounds predicted or calculated to interact with said molecular interaction site;

comparing three dimensional representations of said molecular interaction site with members of the virtual library of compounds to generate a hierarchy of said compounds ranked in accordance with their respective ability to form physical interactions with said molecular interaction site;

synthesizing said highly ranked members of said hierarchy of compounds;

contacting said target RNA with at least one of said highly ranked members to provide a complex between said target RNA and said member or members;

ionizing said complex;

fragmenting said ionized complex; and

determining whether highly ranked member or members bind to said molecular interaction site of said RNA.

34. (Amended) A method of identifying a compound that [modulates activity of] binds to a target RNA comprising:

identifying at least one molecular interaction site on said target RNA, wherein said target RNA comprises single-stranded RNA and is mRNA, pre-mRNA, tRNA, rRNA, or snRNA;

generating *in silico* a virtual library of compounds predicted or calculated to interact

with said molecular interaction site;

comparing three dimensional representation of said molecular interaction site with members of the virtual library of compounds to generate a hierarchy of said compounds ranked in accordance with their respective ability to form physical interactions with said molecular interaction site.

synthesizing the highly ranked members of said hierarchy of compounds;

contacting said target RNA with at least one of said highly ranked members to provide a complex between said RNA and the member or members;

ionizing said complex;

fragmenting said ionized complex; and

determining whether highly ranked member or members binds to said molecular interaction site of said RNA.